



COOPERATIVE STUDIES

Perioperative Myocardial Ischemia in Patients Undergoing Noncardiac Surgery—I: Incidence and Severity During the 4 Day Perioperative Period

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To determine the incidence and characteristics of perioperative myocardial ischemia, the electrocardiographic (ECG) changes consistent with ischemia during the 4 day perioperative period were documented and characterized in 100 patients with or at risk for coronary artery disease undergoing noncardiac surgery. Using continuous two channel ECG monitoring (leads CC_2 and CM_2), the frequency and severity of ECG ischemic episodes defined by ST segment depression ≥ 1 mm or elevation ≥ 2 mm during the preoperative (up to 2 days), intraoperative and early postoperative (first 2 days) periods were compared.

Preoperatively, 28 patients (28%) exhibited 105 episodes of ischemia; intraoperatively, 27 patients exhibited 39 episodes and postoperatively, 42 patients exhibited 187 episodes. There was no difference between the pre- and intraoperative episode characteristics. However, postoperative ischemic episodes were the most severe. The mean ST change was 1.5, 2 and 2.6 mm for pre-, intra- and postoperative episodes, respectively ($p < 0.0001$ postoperative versus pre- or intraoperative); duration of ischemic episodes was 69, 45 and 207 min, respectively ($p < 0.005$ postoperative versus preoperative, $p < 0.001$ versus intraoperative) and area under the ST curve was 88, 74 and 383 mm min ($p < 0.009$ postoperative versus preoperative, $p < 0.005$ versus intraoperative).

Ninety-four percent of all postoperative ischemic episodes were silent; 80% of all episodes occurred without acute change ($\pm 20\%$ of control) in heart rate and 77% of intraoperative episodes occurred without acute change in blood pressure. However, postoperative heart rate was chronically higher (mean 92 versus 76 beats/min preoperative and 71 beats/min intraoperative, $p \leq 0.001$). Patients with coronary artery disease versus those with risk factors alone were equally likely to develop ischemia during any period ($\chi^2 = 0.21$, $df = 2$, $p = 0.60$); 11 of the 13 adverse cardiac outcomes were preceded by postoperative ischemia.

It is concluded that in noncardiac surgical patients with or at risk for coronary artery disease 1) preoperative ischemia is relatively common, occurring equally in patients with documented and potential coronary artery disease; 2) anesthesia and surgery are not associated with an increased incidence or severity of ischemia; 3) ischemia is most frequent and most severe during the postoperative period; and 4) postoperative ischemia is silent, may be related to chronically elevated heart rate and appears to be associated with adverse cardiac outcome.

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Perioperative cardiac morbidity is the leading cause of death after anesthesia and surgery. Approximately 3 million of the 25 million patients who undergo anesthesia and surgery in the United States annually have or are at risk for coronary artery disease (1). The incidence of perioperative cardiac

morbidity in this at-risk population remains high, ranging from 2% to 15% (2).

Early studies (3-7) addressing this problem found that recent myocardial infarction and current congestive heart failure were proven predictors of perioperative morbidity. Subsequently, specialized preoperative testing, including exercise stress testing, dipyridamole thallium imaging and ambulatory electrocardiographic (ECG) monitoring, was recommended for selected subsets of this population (8-12). However, despite the use of such preoperative testing, perioperative cardiac morbidity remained substantial. Recently, it was recognized (2) that in addition to the preoperative disease state, dynamic physiologic changes occurring intra- and postoperatively may also contribute to adverse cardiac outcome. Specifically, perioperative myocardial ischemia, a potentially reversible predictor, has been dem-

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onstrated (13) to be the most important correlate of adverse cardiac outcome after noncardiac surgery.

The incidence and detailed characteristics of perioperative ischemia, however, are generally unknown. Although several studies (2,14,15) addressed intraoperative ischemia, few have accounted for the important preoperative baseline period and no large-scale study has investigated postoperative ischemia rigorously. Accordingly, we determined the incidence and characteristics of myocardial ischemia* over the immediate 4 day perioperative period in at-risk patients undergoing noncardiac surgery.

Methods

Study subjects. We studied 100 men with or at risk for coronary artery disease scheduled for elective noncardiac surgery with general anesthesia at the Department of Veterans Affairs Medical Center in San Francisco. The study protocol was approved by our Committee on Human Research and all patients provided informed consent. Entry criteria included the presence of: 1) definite coronary artery disease indicated by previous myocardial infarction, typical angina or atypical angina with an ischemic ECG response to exercise (16) or scintigraphic evidence of a myocardial perfusion defect (17); or 2) risk for coronary artery disease suggested by previous or current vascular surgery; or 3) the presence of at least two of the following cardiac risk factors (in addition to male gender): age >65 years, hypertension, current smoking, serum cholesterol >240 mg/dl or diabetes mellitus. Typical angina was defined as a history of chest pain having at least three of four characteristics: substernal location, precipitation due to exercise or stress, <15 min duration and resolution after rest or nitroglycerin. Atypical angina required two of these characteristics. Patients with left bundle branch block or an implanted cardiac pacemaker were not eligible. Patients were unselected and not routinely screened using specialized testing such as exercise stress, dipyridamole thallium imaging or coronary angiography. We report on 100 consecutive patients who met entry criteria and had interpretable ECG data during the entire 4 day perioperative period.

General measurements. Research data were collected in parallel to clinical data. The physicians providing patient care were blinded to all research information. Preoperatively, patients were evaluated clinically and their charts reviewed using the guidelines of the Coronary Artery Surgery Study (18). Surgery was classified as: major vascular (n = 42), intraabdominal (n = 21), intrathoracic (n = 5) and

other (orthopedic, neurosurgical, general/plastic and head/neck, n = 32). The primary anesthetic was: halothane (n = 1), isoflurane (n = 17), isoflurane/narcotic (n = 63) and narcotic (n = 19). Intra- and postoperative medications, blood loss, total fluids infused and duration of anesthesia and surgery were recorded. Postoperatively, all patients were examined by a study physician on each day until hospital discharge. All cardiovascular medications were recorded. A 12 lead ECG was obtained preoperatively, daily for the 1st 7 postoperative days, on the 10th and 14th postoperative days, weekly thereafter, on the day of discharge and whenever clinically indicated (shortness of breath, chest pain or syncope). Serum creatine kinase (CK) levels with isoenzymes were determined preoperatively, postoperatively on days 1 and 5 and when clinically indicated, including whenever ECG changes consistent with ischemia or infarction occurred. Serum lactate dehydrogenase (LDH) levels with isoenzymes were obtained on postoperative day 5 and when clinically indicated.

ECG measurements. For up to 2 days preoperatively, intraoperatively and 2 days postoperatively, patients were monitored continuously using a two channel AM ECG recorder (Marquette Electronics, Series 8500). The recorder frequency response is 0.05 to 80 Hz at -3 decibels. Electrodes were silver-silver chloride and skin impedance was <5 k Ω in all patients. Chest leads C₁ and C_M were used (19). Before study, the effect of positional variation on ECG morphology was measured in the supine, left lateral decubitus, right lateral decubitus and upright positions. Postoperatively, each patient was questioned by a study physician for signs and symptoms of ischemia.

Electrocardiographic data were initially processed by a technician and analyzed and verified by two independent investigators (D.M., M.H.) who had no knowledge of patient identity or clinical course. Ambulatory ECG tapes were analyzed for ST segment deviation after excluding all abnormal QRS complexes, such as ventricular ectopic and aberrant beats. A continuous two lead ST segment trend was then generated and all potential ischemic episodes identified. For each episode, the corresponding ECG complexes during the baseline period and during the onset, maximal ST change, maximal heart rate and offset periods were analyzed. The baseline ST segment level was defined as the average ST segment during a stable period (usually 15 to 60 min) preceding each ischemic episode. An ECG ischemic episode was defined as reversible ST segment changes ≥ 1 mm in duration and involving a shift from baseline (adjusted for positional changes) of either ≥ 1 mm (0.1 mV) depression (with slope ≤ 0) or ≥ 2 mm elevation at the J point. The ST segment depression was measured 60 ms after the J point unless that point fell within the T wave, in which case it was shortened to a minimum of J + 40 ms. If T wave changes occurred with ST depression, we also required that the J point fall below baseline. For each episode, we measured: 1) duration, 2) maximal ST change, 3) ST slope, 4) heart rate (at baseline, onset, maximal ST change and

*In the absence of an absolute reference standard, we cannot state that ST segment abnormalities truly indicate myocardial ischemia. Although alterations in myocardial perfusion have been documented during silent ischemic episodes (39-41), nonspecific ST segment changes may occur as a result of changes in body temperature, serum electrolytes, ventilatory or positional changes or administration of drugs (42). However, the strong relation we observed between ST abnormalities and the subsequent development of cardiac outcomes suggests the predictive validity of ST abnormalities.

offset), 5) area under the ST curve (20), and 6) associated clinical symptoms and signs.

Hemodynamic measurements. Heart rate was continuously recorded by ambulatory ECG monitoring throughout the 4 day study period. After classification of the QRS complexes and elimination of spurious noise, the QRS class and the timing of the peak of each R wave were analyzed and the artifact-free heart rate was calculated. Systemic blood pressure was recorded continuously from a radial arterial catheter (27 patients) or every 3 min by automated cuff, beginning 30 min before entrance into the operating room until 1 h after surgery. Blood pressure data were screened for spurious values (such as arterial line flushing), stored on hard disk and analyzed. Hypertension (hypotension) was defined as systolic blood pressure >160 (<90) mm Hg for ≥ 5 min, and tachycardia (bradycardia) as a heart rate >100 (<50) beats/min.

Clinical care. Clinical decisions (preoperative medications, monitoring, anesthetic drug, therapy) were not controlled by study protocol. Routinely, all cardiac medications were continued until the morning of surgery. Intraoperatively, routine clinical monitors included a three to five lead ECG, blood pressure (invasive or noninvasive) monitoring, pulse oximetry and mass spectroscopy. Ventilation was controlled until tracheal extubation. Hemodynamic variables were controlled by the anesthesiologist: 7% of all heart rates were >100 beats/min, 8% of systolic blood pressures were >160 mm Hg and 4% of systolic blood pressures were <90 mm Hg. Postoperatively, 65 patients were admitted directly to the intensive care unit and 35 to the recovery room. Therapy for acute postoperative surgical pain consisted of intravenous narcotics (72 patients), intrathecal or epidural narcotics (25 patients) or intrapleural narcotics (3 patients). Cardiac medications were resumed as soon as the patient was able to ingest fluids orally, usually on the morning of the first postoperative day. The dose and time of administration of vasodilators, vasopressors, and inotropic agents were measured, but their use was not controlled. The mean in-hospital stay was 15 ± 13.2 days.

Outcome measurements. All patients were examined by a study physician each day for the first 7 postoperative days, on the 10th and 14th postoperative days, weekly thereafter, on the day of discharge and whenever clinically indicated. Adverse outcomes were detected by study physicians and validated by two investigators (W.B., D.M.) who had no knowledge of the patients' clinical and monitoring data; disagreements were resolved by consensus, involving a third investigator (M.H.) if necessary. As specified in our protocol, outcomes were defined in the following order of severity: cardiac death, nonfatal myocardial infarction, unstable angina, congestive heart failure and ventricular tachycardia. Cardiac death was diagnosed if the patient died from either an arrhythmia or congestive heart failure caused primarily by a cardiac condition. Myocardial infarction required: 1) an elevation of the CK MB isoenzyme (≥ 50 U/liter); 2) the development of either new Q waves (as defined by the

Minnesota Code: 11, 2 [21]) or persistent ST-T wave changes (Minnesota Code: IV, V [21]); or 3) necropsy evidence of acute infarction. (Two investigators blinded to all clinical data read all ECGs (M.L., J.M.H.).)

Unstable angina required severe precordial chest pain that was: 1) nonsurgical, lasting ≥ 30 min; 2) unresponsive to standard therapeutic maneuvers (nitroglycerin, rest); and 3) associated with transient ST segment or T wave changes without development of Q waves or diagnostic enzyme abnormalities. **Congestive heart failure required:** 1) symptoms or signs of pulmonary edema (shortness of breath, rales) documented by chest radiography (vascular redistribution, interstitial edema, alveolar edema); 2) signs of new left or right ventricular failure (cardiomegaly, third heart sound (S₃), jugular venous distention, peripheral edema); and 3) a change in medication involving at least treatment with diuretic drugs. **Ventricular tachycardia** required 5 or more consecutive beats at a rate of ≥ 100 beats/min (22).

Data analysis. Chi-square analysis with continuity correction was applied to categorical data. Student's *t* test was used to test the difference between the mean values in two groups. Multivariate analysis of variance using repeated measures was used to detect differences among periods (pre-, intra- and postoperative). If significant, pairwise comparison using Student's *t* test was used to determine differences among specific periods (23,24). Episode characteristics (such as duration) were compared over the three periods by first averaging the durations of all episodes for each patient for each period and then using multivariate analysis as described. A *p* value <0.05 (two-sided) identified statistically significant differences. Results are expressed as the mean ± 1 SD unless otherwise indicated.

Results

Demographics. Table 1 summarizes the demographic and clinical characteristics of the 100 study patients. They were generally middle-aged or elderly men with coronary artery disease or risk factors for coronary artery disease, such as cigarette smoking or hypertension. The most common type of surgery was vascular, with most operations having a relatively long duration.

ECG findings. Over the 4 day study period, the total ECG monitoring time was 5,901 h. Patients were continuously monitored for 59 ± 17.1 h: 18.6 ± 13.7 h preoperatively, 5.9 ± 2.7 h intraoperatively and 34.4 ± 9.8 h postoperatively. An example of the ECG trend curves and complexes is given in Figure 1. Electrocardiographic changes suggestive of myocardial ischemia ("ischemic episodes"—see Limitations) occurred throughout all periods (Fig. 2).

Fifty-four patients (54%) had ischemia during any period. Relative to the preoperative period, the intraoperative period had a similar incidence of ischemia, fewer ischemic episodes and no greater severity of ischemia (Table 2). The postoperative period had the highest incidence (number of

Table 1. Preoperative Demographics and Clinical Data From 100 Patients

Definite coronary artery disease (%)	59
At risk for coronary artery disease (%)	41
Cardiac history (%)	
Previous myocardial infarction	43
Typical angina	49
History of arrhythmia	25
History of congestive heart failure	11
Cardiac risk factors (%)	
Current smoking	79
Hypertension	61
Diabetes mellitus	30
Age ≥ 65 yr	66
Preoperative antianginal medication (%)	
Nitrates	33
Calcium blocker	21
Beta-adrenergic blocker	20
Any of the above	51
Age (yr)	$67.5 \pm 8.0^*$ (range 40–85)
Duration of anesthesia and surgery (h)	$5.0 \pm 2.6^*$ (range 0.9–12.8)
Primary anesthetic (%)	
Isoflurane-narcotic	63
Narcotic	19
Isoflurane	17
Halothane/narcotic	1
Type of surgery (%)	
Vascular	42
Intraabdominal	21
Intrathoracic	5
Other	32

*Mean \pm SD

patients, episodes) and greatest severity of ischemia (ischemic min/h monitored, area under the ST curve/h). The specific episode characteristics were compared in the 54 patients who had ischemia during any period (Table 2). (If a patient had more than one episode in a period, the episode with the greatest ST change was chosen.) Postoperative episodes were the most severe as assessed by either: maximal ST change, duration, area under the ST curve or ischemic burden (ischemia min/h monitored). There was no difference between the pre- and intraoperative characteristics. The postoperative period also had significantly more patients with episodes having maximal ST change ≥ 2 mm (9, 18, 26 patients, respectively) or duration ≥ 30 min (17, 10 and 28 patients, respectively). Postoperative ischemia was clinically silent; in patients able to communicate such symptoms postoperatively, 94% of all episodes were unaccompanied by any cardiac symptoms (angina, pulmonary congestion or syncope).

Relation of ischemia to hemodynamics. Mean heart rate was higher in the postoperative period (Fig. 3) than in either the pre- or intraoperative period ($p < 0.05$). Ischemic episodes were preceded by acute increases in heart rate ($\geq 20\%$) in only 27% of preoperative, 26% of intraoperative and 14%

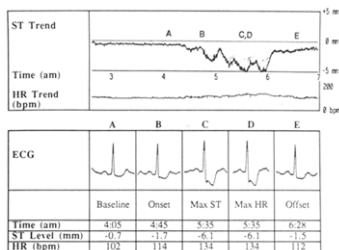


Figure 1. Example of ambulatory ST trend in electrocardiographic (ECG) channel one (CM₁) for one ischemic episode. Shown are the ECG complexes measured at the J point + 60 mm for: A = baseline, the most stable period before the episode; B = onset, where the ST level is ≥ -1 mm from baseline; C = maximal (Max) change in ST level; D = maximal heart rate (HR) coincides with the maximal ST change; E = offset, when the ST level is < -1 mm change from baseline.

of postoperative episodes. Similarly, intraoperative ischemic episodes were preceded by acute increases in blood pressure ($\geq 20\%$) in only 15% of episodes and by acute decreases in blood pressure in only 8% of episodes.

Relation of ischemia to risk factors and outcome. Ischemia during any period was equally common among patients with definite coronary artery disease (56%) or risk factors for coronary artery disease (51%) (chi-square = 0.21, df = 2, $p = 0.60$). There was no difference in the incidence of ischemia in patients undergoing major vascular surgery (60%) versus abdominal/thoracic surgery (54%) versus other

Figure 2. Incidence and severity of ischemia during the preoperative (PREOP), intraoperative (INTRAOP) and postoperative (POSTOP) periods. Shown are the total number of episodes per period and the number of patients (Pts.) with ischemia during each period. The severity of ischemia is shown as the number of episodes with an ST change from baseline of $\geq +2$ mm (elevation) and ≥ -1 to -1.9 , ≥ -2 to -2.9 and ≥ -3 (depression). The ST change was calculated by subtracting the baseline ST level from the maximal ST level.

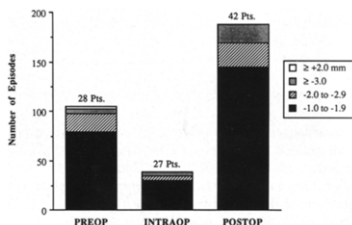


Table 2. Characteristics of Perioperative Ischemia

	Preoperative	Intraoperative	Postoperative
General characteristics of ischemia			
Total hours monitored	1,864	592	3,443
No. of patients with ischemia	28	27	42
No. of ischemic episodes	105	39	187
Total ischemic minutes	4,482	1,423	15,459
Ischemic min/h monitored	2.4	2.4	4.5
Area under the ST curve (mm \times min) h monitored	3.2	1.7	8.1
Ischemic episode characteristics			
ST change (mm)			
Mean	-1.5 \pm 1.5	-2.0 \pm 0.9	-2.6 \pm 1.5*
Median	-1.6	-2.0	-2.3
Duration (min)			
Mean	69 \pm 66	45 \pm 59	207 \pm 350†
Median	46	24	51
Area under the ST curve* (mm min)			
Mean	88 \pm 92	74 \pm 124	383 \pm 764‡
Median	51	27	69
Ischemic min/h monitored			
Mean	3.4 \pm 6.7	3.7 \pm 6.8	8.6 \pm 14.6§
Median	0.2	0.1	1.9
Percent with \geq 20% increase in heart rate	27	26	34

*p < 0.0001 for post- vs preoperative; p < 0.0001 post- vs intraoperative; †p < 0.005 for post- vs preoperative; ‡p < 0.001 post- vs intraoperative; §p < 0.009 for post- vs preoperative; p < 0.005 post- vs intraoperative; §p < 0.005 for post- vs preoperative; p < 0.007 post- vs intraoperative.

surgery (43% orthopedic, neurosurgical, head/neck, peripheral vascular) (chi-square = 1.2, df = 2, p = 0.60). There also was no difference in the incidence of perioperative ischemia in patients who received preoperative antianginal medication (nitrates, beta-adrenergic blockers, calcium channel blockers) versus those who did not (51% versus 45%, chi-square = 0.17, df = 2, p = 0.70).

Thirteen (13%) of the 100 patients had an adverse in-hospital cardiac outcome: fatal myocardial infarction in 1, nonfatal myocardial infarction in 3, unstable angina in 1, congestive heart failure in 4, and ventricular tachycardia in 4. Eleven of the 13 adverse outcomes were preceded by postoperative ischemia (9 by preoperative ischemia, 9 by intraoperative ischemia). Two of the three nonfatal myocar-

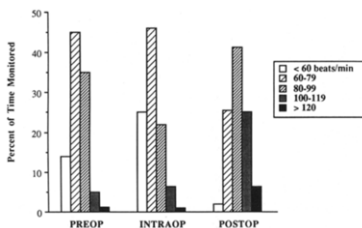
dial infarctions and all four congestive heart failure outcomes were detected clinically. The ventricular tachycardia episodes were asymptomatic.

Discussion

Our findings suggest that in at-risk patients undergoing noncardiac surgery 1) preoperative ECG changes suggestive of ischemia are relatively common, occurring equally in patients with coronary artery disease and in those with risk factors alone; 2) intraoperative ischemia is similar in incidence and severity to preoperative ischemia, suggesting that anesthesia and surgery may not be as stressful as previously thought; and 3) postoperative ischemia is greatest in incidence and severity, but difficult to detect because of its silent nature. Although we consider our outcome results preliminary, they suggest that postoperative ischemia may be associated with an adverse cardiac outcome.

Preoperative ischemia. The preoperative incidence of ischemia was 28% in our study patients with definite or probable coronary artery disease. In ambulatory patients, the reported incidence rate of preoperative ischemia in these subgroups varies markedly, being 2.5% to 10% in apparently healthy asymptomatic middle-aged men (25), approximately 30% after acute uncomplicated myocardial infarction and approximately 60% (range 46% to 100%) in patients with chronic stable angina (26-31). The inhomogeneity of our study group makes it difficult to compare our preoperative incidence with these rates. Our results, however, are consistent with several recent findings in patients undergoing

Figure 3. Heart rate distribution for the three perioperative periods. Abbreviations as in Figure 2.



vascular surgery (14,15). Our finding that the preoperative incidence of ischemia did not differ in patients with coronary artery disease versus those patients at risk suggests that it is difficult to assess the preoperative ischemic state using routine testing.

Intraoperative ischemia. Our 27% incidence of intraoperative ischemia appears to be low, nearly equalling the preoperative incidence. The intraoperative period has many stresses that may affect myocardial oxygen demand and supply, including changes in catecholamine levels, temperature and respiration, shifts in intravascular and interstitial fluid and direct surgical and anesthetic effects (19). The changes in intraoperative blood pressure, heart rate and ventricular function associated with these stresses may precipitate ischemia. However, in our study, intraoperative hemodynamics were well controlled, with a <10% incidence of tachycardia, hypertension or hypotension and only 28% of ischemic episodes associated with a $\geq 20\%$ change in heart rate or blood pressure. That our intraoperative incidence of ischemia was no higher than that before operation implies that with such hemodynamic control, anesthesia and surgery in themselves may not be as stressful as previously thought. We attribute this to the substantial advances made over the last decade in intraoperative cardiovascular monitoring and therapy, as well as the development of anesthetic techniques and new anesthetic agents (2). Our findings regarding this apparent intraoperative "recapitulation" of the preoperative ischemic pattern are consistent with our recent findings in patients undergoing cardiac surgery (32).

Postoperative ischemia. The incidence and severity of ischemia were greatest during the postoperative period. During the 1st 2 days after surgery, 42% of patients developed 187 episodes of ST changes consistent with ischemia, compared with 28% having 105 preoperative episodes and 27% with 39 intraoperative episodes. In addition, the ischemic minutes and area under the ST curve/monitored were two- to fivefold higher postoperatively than during the preoperative or intraoperative periods. Individual postoperative ischemic episodes also were more severe (ST change, ischemia min/h monitored) and tended to be longer.

There are several possible causes of postoperative ischemia and some may be reversible. Numerous stresses occur during the postoperative period, including major changes in adrenergic activity, plasma catecholamine levels, body temperature, pulmonary function, fluid balance, sleep patterns and pain perception (32-34). The substantial increase in heart rate in our patients throughout the postoperative study is consistent with these stresses and may be attributed to any or all of them. It could have had a cumulative effect that altered myocardial oxygen demand (and supply), thereby precipitating ischemia. Other factors may primarily affect oxygen supply, such as hypotension, platelet activation with mediator release, coagulation abnormalities and changes in arachidonic acid metabolism (2). Unfortunately, few data are available for distinguishing the role of these abnormalities in producing ischemia. More aggressive postoperative pain

control and beta-blocker or antianginal therapy may be indicated during the early postoperative period.

Postoperative ischemia was not only relatively common and persistent, but also silent, making it difficult to detect using the usual clinical modalities. Ninety-four percent of postoperative episodes were clinically silent, unaccompanied by symptoms of angina, pulmonary congestion or syncope. This silent nature is not surprising. Ambulatory patients with silent ischemia appear to have abnormal somatic pain thresholds and altered pain perception (25,35-37). After surgery, a number of factors, such as residual anesthetic effects, administration of analgesic agents and competing somatic stimuli (for example, incisional pain), may further alter pain perception and differentiation. These effects may explain why postoperative patients have a higher incidence rate of painless myocardial infarction (50% to 70%) than nonsurgical patients (20% to 40%) (2,25,32,38). Therefore, should postoperative ischemia prove to be an important reversible predictor of outcome, its detection will require a reassessment of our current postoperative monitoring and treatment protocols.

Other relations. Two other findings are interesting. First, the lack of a relation between the presence of coronary artery disease and the occurrence of ischemia is surprising. All patients had definite coronary artery disease or one or more risk factors predisposing to coronary artery disease. However, their chronic disease state was stable, without the presence of unstable angina, acute myocardial infarction or acute congestive heart failure. Perhaps, with stable chronic disease, differences between the actual presence of coronary artery disease and risk factors for coronary artery disease are less important than the effects of the dynamic physiologic changes that occur intra- and postoperatively. Second, although the number of adverse outcomes was small (13 of 160 patients), almost all (11 of 13 patients) were preceded by postoperative ischemia. These data must be considered preliminary, but suggest a relation between postoperative ischemia and adverse cardiac outcome and are supported by recent findings (13). Thus, postoperative monitoring and treatment of selected patients may be warranted. Further study is necessary to define such high risk subgroups.

Limitations. We cannot state whether ST segment abnormalities observed on ambulatory ECG monitoring truly indicate myocardial ischemia. An absolute reference standard does not exist and, even if available, would be difficult to apply because of the spontaneous occurrence of perioperative ischemia. Changes in myocardial perfusion and ventricular function have been documented during silent ischemic episodes (39-41), but nonspecific ST segment changes may occur perioperatively as a result of changes in body temperature, serum electrolytes, ventilation or body position or drugs administered. Establishing the predictive importance of perioperative ST segment abnormalities may be the only way to ascertain their ischemic "validity."

Our outcome ascertainment system concentrated on the early postoperative period when adverse cardiac events are

most frequent. On each of the 1st 7 days after surgery, a study physician examined each subject, reviewed the medical record of the preceding day and obtained and scrutinized a 12 lead ECG. Creatine kinase and isoenzyme levels were measured on postoperative days 1 and 5 and LDH were measured on postoperative day 5; both sets of enzymes were also obtained whenever clinically indicated (for example, chest pain) or if the ECG was consistent with ischemia or infarction. This system could have missed an asymptomatic event characterized by increase in cardiac enzymes on, for example, day 3 in which ECG changes were transient (<24 h) and in which cardiac enzymes were normal when tested on day 5. Such an event, however, would not have met our diagnostic criteria for myocardial infarction, which required persistent ECG changes in the absence of symptoms.

The high incidence of postoperative ischemia presents a challenging problem if detection and treatment of such ischemia are proven important. The costs may be prohibitive unless preoperative risk stratification enables identification of at-risk subgroups. We did not perform such stratification using specialized testing (exercise stress, dipyridamol thallium, coronary angiography). Studies are underway to identify such subgroups.

Conclusions. Our results suggest that ECG ST changes indicative of myocardial ischemia occur throughout the pre-, intra- and postoperative periods in patients with and at risk for coronary artery disease undergoing elective noncardiac surgery. Anesthesia and surgery do not appear to be associated with an increased incidence or severity of ischemia, suggesting that they may be less stressful than previously thought. Instead, the incidence and severity of ischemia were greatest during the postoperative period, which also was characterized by chronic tachycardia. Therefore, the postoperative period may warrant special attention, including therapeutic trials to determine whether extended monitoring and aggressive therapy for control of pain and heart rate are warranted during the 1st 2 days after surgery.

Appendix

The SPI (Study of Perioperative Ischemia) Research Group consists of:

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Data Management: Ida M. Tateo, MS; Jeffrey Tice, BS; Cary Fox, MA; Angela Heithaus, BS (former).

Consultants: Jonathan Showstack, PhD; Diana C. Nicoll, MD, PhD; Paul Henneken, MD; Barry Massie, MD.
Policy and Data Monitoring Board: Kanu Chatterjee, MB, FRCP, H. Barrie Farley, MD; Lawrence W. Way, MD; Warren Winkelstein, MD, MPH (Chairman).

References

- National Center for Health Statistics: Health, United States, 1988, DHHS Pub. No. (PHS) 89-1232. Public Health Service, Washington, DC: U.S. Government Printing Office, March 1989:10-7, 66, 67, 100, 101.
- Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990;72:153-84.
- Master AM, Dack S, Jaffe HL. Postoperative coronary artery occlusion. *JAMA* 1938;110:1415-8.
- Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;297:845-50.
- Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. *JAMA* 1978;239:666-70.
- Rao TK, Jacobs KH, El-Eit AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology* 1983;59:499-505.
- Foster ED, Davis KB, Carpenter JA, Abele S, Fray D. Risk of noncardiac operation in patients with defined coronary disease: the Coronary Artery Surgery Study (CASS) Registry experience. *Ann Thorac Surg* 1986;41:42-5.
- Carliner NH, Fisher ML, Plotnick GD, et al. Routine preoperative exercise testing in patients undergoing major noncardiac surgery. *Am J Cardiol* 1985;56:51-7.
- Boucher CA, Brewster DC, Darling CR, Okada RD, Strauss WH, Polost GM. Determination of cardiac risk by dipyridamol-thallium imaging before peripheral vascular surgery. *N Engl J Med* 1985;312:389-94.
- Cutler BS, Leppo JA. Dipyridamol thallium 201 scintigraphy to detect coronary artery disease before abdominal aortic surgery. *J Vasc Surg* 1987;5:91-100.
- Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. *Ann Intern Med* 1989;110:659-66.
- Raby KE, Goldman L, Creager MA, et al. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989;321:1296-300.
- Mangano DT, Browner WS, Hollenberg M. Cardiac morbidity and mortality following noncardiac surgery: the role of perioperative ischemia. *N Engl J Med* 1990;323:1781-8.
- Raby KE, Goldman L, Creager ME, Selwyn AP. Detection of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery (abstr). *Circulation* 1988;78(suppl II):II-333.
- Ouyang P, Gerstenblith G, Furman WR, Golubev PJ, Gottlieb SO. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol* 1989;64:1113-6.
- Chamman BR, Waters DD, Bourassa MG, Tubau JF, Wagnart P, Ferguson RJ. The importance of clinical subsets in interpreting maximal treadmill exercise test results: the role of multiple-lead ECG systems. *Circulation* 1979;59:580-7.
- Ashburn WL, Tubau JF. Myocardial perfusion imaging in ischemic heart disease. *Radiol Clin North Am* 1980;18:467-86.
- Coronary Artery Surgery Study (CASS). Manual of operations. II. Data collection and storage; collaborative studies in coronary artery surgery. Washington, DC: National Heart, Lung and Blood Institute, prepared by the CASS Coordinating Center, University of Washington, Seattle, 1978.
- London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. *Anesthesiology* 1988;69:232-41.
- Hollenberg M, Zolnick JM, Go M, et al. Comparison of a quantitative treadmill exercise score with standard electrocardiographic criteria in screening asymptomatic young men for coronary artery disease. *N Engl J Med* 1985;313:600-6.
- Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies: classification systems. *Circulation* 1960;21:1160-75.

22. Zipes DP. Specific arrhythmias: diagnosis and treatment. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 2nd ed. Philadelphia: WB Saunders, 1984:683-743.
23. Zar JH. *Biostatistical Analysis*. Englewood Cliffs, NJ: Prentice-Hall, 1974:259-61, 291-5.
24. Cox DR. *The Analysis of Binary Data*. London: Methuen, 1970.
25. Cohn PF. Silent myocardial ischemia. *Ann Intern Med* 1988;109:312-7.
26. Theroux P, Waters DD, Halphen C, Dehaes JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979;301:344-5.
27. Deanfield H, Maseri A, Selwyn AP, Chierchia S, Ribeiro P, Krakler S, Morgan M. Myocardial ischemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. *Lancet* 1983;2:751-8.
28. Cecchi AC, Davellini EV, Marchi F, Pucci P, Santoro GM, Fazzini PF. Silent myocardial ischemia during ambulatory electrocardiographic monitoring in patients with effort angina. *J Am Coll Cardiol* 1983;1:934-9.
29. Tzivoni D, Gavish A, Benhoni J, Keren A, Stern S. Myocardial ischemia during daily activities and stress. *Am J Cardiol* 1986;58:47B-50B.
30. Gottlieb SO, Weisfeldt ML, Quyang P, Mellis ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med* 1986;314:1214-9.
31. Carboni GP, Lahiri A, Cushman PM, Rafferty EB. Ambulatory heart rate and ST-segment depression during painful and silent myocardial ischemia in chronic stable angina pectoris. *Am J Cardiol* 1987;59:1029-34.
32. Knight AA, Hollenberg M, London MJ, Mangano DT, SPI Research Group. Myocardial ischemia in patients awaiting coronary artery bypass grafting. *Am Heart J* 1989;117:1189-96.
33. Siliciano D, Mangano DT. Postoperative myocardial ischemia: mechanisms and therapies. In: Estafanoou FG, ed. *Opioids in Anesthesia II*. Boston: Butterworth, 1990:164-76.
34. Uekelman R, Norton JA, Jelenich SE, et al. Responses of the hypothalamic-pituitary-adrenal and renin-angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. *J Clin Endocrinol Metab* 1987;64:986-94.
35. Droste C, Roskamm H. Experimental pain measurement in patients with asymptomatic myocardial ischemia. *J Am Coll Cardiol* 1983;1:940-5.
36. Glazier JJ, Chierchia S, Brown MJ, Maseri A. Importance of generalized defective perception of painful stimuli as a cause of silent myocardial ischemia in chronic stable angina pectoris. *Am J Cardiol* 1986;58:667-72.
37. Epstein SE, Quyyumi AA, Bonow RO. Myocardial ischemia—silent or symptomatic. *N Engl J Med* 1988;318:1038-43.
38. Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction: an update on the Framingham Study. *N Engl J Med* 1984;311:1144-7.
39. Cohn PF, Brown EJ Jr, Wynne J, Holman BL, Atkins HL. Global and regional left ventricular ejection fraction abnormalities during exercise in patients with silent myocardial ischemia. *J Am Coll Cardiol* 1983;1:931-3.
40. Chierchia S, Lazzari M, Freedman B, Brunelli C, Maseri A. Impairment of myocardial perfusion and function during painless myocardial ischemia. *J Am Coll Cardiol* 1983;1:924-30.
41. Deanfield JE, Shea M, Ribeiro P, et al. Transient ST-segment depression as a marker of myocardial ischemia during daily life. *Am J Cardiol* 1984;54:1195-1200.
42. Knight AA, Hollenberg M, London MJ, et al. Perioperative myocardial ischemia: importance of the preoperative ischemic pattern. *Anesthesiology* 1988;68:681-8.